REMARKS

Claims 1, 8, 10-16, 33 and 34 are pending. Claim 1 has been amended. No new matter has been added.

The Applicant thanks the Examiner for withdrawing the some of the previous rejections under 35 U.S.C. §112, first paragraph and the rejection under 35 U.S.C. §102.

Rejection Under 35 U.S.C. §112, second paragraph

Claims 1, 8, 10-16, 33-34 are rejected under 35 U.S.C. §112, second paragraph as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

In particular, claims 1, 3-16 and 33-34 are rejected because "claim 1 does not recite that the reference standard is PSMA expression levels in a primary tumor of a subject diagnosed with prostate cancer that does not have recurrence."

Claim 1 has been amended to recite that the reference standard is PSMA expression levels in a primary tumor of subjects diagnosed with prostate cancer that do not have recurrence. The amendment to claim 1 obviates this rejection. Therefore, the Applicant respectfully requests that the Office withdraw this rejection.

Rejection Under 35 U.S.C. §112, first paragraph

Claims 1, 8, 10-16 and 33-34 are rejected under 35 U.S.C. §112, first paragraph "for lack of enablement for a method of determining if a subject is **at risk of prostate cancer recurrence**." The Office alleges that "one cannot predict the level of PSMA in prostate cancer is predictive of prostate cancer recurrence, and validation of the claimed method in a tested population is necessary..."

Applicant respectfully traverses this rejection. The Applicant notes that the claims as amended recite that the sample is from a primary tumor of a subject obtained upon diagnosis of prostate cancer. Applicant has clearly provided sufficient evidence of the correlation between

PSMA expression levels in a primary tumor at the time of diagnosis and risk of recurrence in those subjects diagnosed with prostate cancer at a later date.

Applicant demonstrated that PSMA expression is an independent predictor of prostate cancer recurrence. The present application describes univariate and multivariate analysis of biopsy samples from one hundred and thirty six patients who underwent a radical prostatectomy. The Applicant determined PSMA expression levels at the time of the prostatectomy using an automated system and tracked those patients to determine which patients had prostate cancer recurrence. From this data, Applicant demonstrated that PSMA expression levels at the time of diagnosis significantly differ between patients that later have recurrence and those who do not. Applicant's position is discussed in more detail below.

I. Applicant's findings have been confirmed.

Applicant determined PSMA expression levels from biopsy samples obtained from patients at the time of diagnosis of prostate cancer and then followed those patients to determine if the patient suffered from prostate cancer recurrence. The Applicant determined PSMA expression levels using an automated system. The data compiled included information regarding recurrence in patients diagnosed with prostate cancer as early as 1987. Applicant was able to demonstrate, using univariate and multivariate statistical analysis, that PSMA levels at the time of diagnosis of prostate cancer correlate with recurrence of prostate cancer in patients that showed increased PSMA expression levels at the time of diagnosis. Applicant's multivariate analysis confirmed that PSMA expression levels provided an independent prediction of prostate cancer recurrence.

Applicant's results were confirmed by Perner et al. Perner et al. analyzed PSMA expression levels of 93 men diagnosed with prostate cancer who underwent a radical prostatectomy. PSMA expression levels were determined at the time of diagnosis using an automated system. The data compiled included information regarding recurrence in patients diagnosed with prostate cancer as early as 1986. Perner et al., using univariate and multivariate analysis, corroborated Applicant's finding that increased PSMA expression levels at the time of

diagnosis correlate with increased risk of recurrence. Perner et al. also conclude (at page 700, last paragraph) that "PSMA expression in primary tumor ***independently predicts*** disease outcome not only in a PSA-screened cohort but also in a high risk population." (***emphasis added***).

II. The Applicant demonstrated that PSMA expression levels are predictive of prostate cancer recurrence for any prostate cancer population, including those with low grade cancer.

To support is allegation that additional validation studies are necessary, the Office states

> the claims encompass PSMA predictive value for any prostate cancer population, including those with low grade prostate cancer. The specification only disclose PSMA data for those with a mean value of Gleason scores 6.33 … to arrive at the predictive value (p.33). It is well known in the art that the severity of prostate cancer is correlated with Gleason scores, from 2 to 10, where in score of 10 is the most advanced. … Bostwick et al, however, teach those having Gleason scores of 3, 4 and 5 do not have recurrence within the minimum patient follow -up period of 4.5 years.

The Office appears to be assuming that because the ***average*** Gleason score reported by the Applicant was 6.33, patients with low grade prostate cancer were not evaluated. This is incorrect. As provided on page 33 of the application, the conclusions drawn by the Applicant were based upon data obtained from patients of which about half (56%) had low grade tumors (Gleason score $\leq$6) and about half (44%) had high-grade tumors (Gleason score >7). The 6.33 relied upon by the Office is merely the average Gleason score for these two patient populations. Therefore, Applicant's findings were based upon data obtained from patients having various Gleason scores including those patients with low grade cancer.

Perner et al. also obtained their data from patients having various Gleason scores. The patient population evaluated by Perner et al. included 20 patients having a Gleason score of 2-6, 28 patient having a Gleason score of 7, and 45 patients having a Gleason score of 8-10. (see Table 2 of Perner et al.). Therefore, the data relied upon by Perner et al., which corroborates Applicant's findings, was based upon data obtained from patients having various Gleason scores including those patients with low grade cancer.

Thus, Applicant's findings and the findings of Perner et al. show that increase PSMA levels at the time of diagnosis of prostate cancer correlate with an increased risk of recurrence for patients having low and high grade prostate cancer.

III. Applicant does not agree with the Office's characterization of Perner et al.

At page 7 of the Office Action, the Office makes several comments about Perner et al. that the Applicant would like to address.

First, the Office alleges that "Perner et al. do not have any follow up studies after the therapy to determine the number of actual recurrence."

Applicant disagrees with this assertion. Perner et al. evaluated patients' PSMA expression levels from tissue samples obtained by an initial prostatectomy and then followed the patients' status for several years after the prostatectomy to determine if there was prostate cancer recurrence in any of the patients. See, for example, page 697, column 2 of Perner et al. which provides:

> For all cases, the Hybritech platform … was used for serum PSA level measurement before surgery …, then every 6 months after the surgery during the first two years, and at least yearly afterward (mean [maximum] follow up: 2.8 [7.7] years). PSA failure was defined as serum PSA levels greater than 0.4 ng/mL during follow up, and the earlier date of 2 consecutive increments was defined as date of failure.

PSA failure as described by Perner et al. is prostate cancer recurrence. See, e.g., page 31 of the application which states "a post-surgical elevation of the PSA level from a base line of 0 ng/ml to greater than 0.4 ng/ml on two consecutive occasions was considered as biochemical evidence of recurrence." Thus, the results reported by Perner et al., which corroborate Applicant's findings, were based upon data that included PSMA expression levels at the time of diagnosis and a follow up analysis of the patients to determine if there was prostate cancer recurrence.

The Office also argues that Perner et al. disclose that "stratified according to Gleason score, PSMA expression is not an independent predictor of PSA recurrence."

Applicant does acknowledge that Perner et al. make the statement recited by the Office; however, when reviewed in context, this statement by Perner et al. does not contradict Applicant's findings. The statement relied upon by the Office can be found in the paragraph bridging page 699 and page 700 of Perner et al. It is clear that this paragraph discusses the results obtained using univariate statistical analysis. However, Perner et al. also studied the correlation between prostate cancer recurrence and PSMA expression levels using multivariate analysis. Multivariate statistical analysis allows for the determination of independent contribution of the parameters evaluated. Based upon the combination of univariate analysis and multivariate analysis, Perner et al. conclude that "PSMA expression in primary tumor ***independently*** predicts disease outcome not only in a PSA-screened cohort but also in a high risk population." (***emphasis added***).

Therefore, the findings reported by Perner et al. are consistent with Applicant's findings that PSMA expression levels at the time of diagnosis independently predicts disease recurrence.

IV. Thomas et al. and Beckett et al. were not analyzing the same problem as the Applicant, Perner et al. or Bostwick et al.

The Office alleges that "the teaching of Bostwick et al. is reinforced by the teachings of Beckett et al and Thomas et al, all of record, that the level of serum PSMA in a prostate cancer patient is not a predictor of prostate cancer recurrence."

The Applicant disagrees. Neither Beckett et al. nor Thomas et al. evaluated PSMA expression levels at the time of diagnosis to make a prediction about recurrence at some later date. Beckett et al. and Thomas et al. evaluated PSMA expression in serum as a marker of advanced disease at the time the sample was taken. This is a different issue than the one evaluated by the Applicant, Perner et al. and Bostwick et al. Therefore, Beckett et al. and Thomas et al. do not reinforce the teachings of Bostwick et al.[1]

[1] Applicants also note that in arguing the relevance of Beckett et al. and Thomas et al. the Office states that "serum PSMA reflects the severity of the disease, and thus the level of PSMA in primary prostate cancer tissue." However, the Office has provided no evidence that more PSMA in primary cancer tissue correlates to more PSMA present in the serum.

V. The only other evidence of record that contradicts Applicant's findings is based upon subjective evaluation of PSMA expression levels, a technique which has been acknowledged may skew results.

The Office continues to allege that validation of Applicant's findings is necessary because "the teaching in the art is **contradictory** concerning whether PSMA level is predictive of recurrence in prostate cancer." The only remaining reference relied upon by the Office to support the allegation of contradicting results is Bostwick et al.

Bostwick et al., a reference that published more than ten years ago, relied upon subjective evaluation of PSMA expression levels to arrive at its conclusions. See, e.g., page 2258, first full paragraph of Bostwick et al. which states that "the extent and intensity of staining for each antibody [to determine PSMA expression levels] ***was evaluated subjectively*** in benign epithelium, high grade PIN, and adenocarcinoma by two authors." (***emphasis added***). As provided in Perner et al. at page 700, second column, many inconsistencies in the art regarding PSMA expression "may be due to different antibodies and evaluation of PSMA." To avoid this problem, both the Applicant and Perner et al. used automated systems to evaluate PSMA expression levels. See, e.g., Perner et al. which states "to avoid subjective evaluation of the PSMA expression within our study, we performed objective evaluation with a semi-automated quantitative approach ...." Based upon this objective data, both the Applicant and Perner et al. conclude that PSMA expression levels, at the time of diagnosis, independently predicts disease recurrence.

The arguments made by the Office emphasize that because there are allegedly contradicting results, validation studies are required. See, e.g., page 6, lines 4-7 of the Office Action. However, there is only one reference of record, namely Bostwick et al., that suggests that there are contradictory results and as discussed above, this reference, unlike the evidence provided by the Applicant and Perner et al. (which corroborate Applicant's findings), is based upon subjective data.

VI. The remaining references cited by the Office regarding validation studies involved an analysis of markers in a different context.

The Office continues to cite the Tockman et al. and the Vandesompele et al. references to support its assertion that validation studies are necessary.

As discussed in previous replies, both of these references are analyzing proteins as **predictive markers for early detection of primary cancers** and not for **recurrence in a patient population diagnosed with a cancer**. For example, Tockman et al. were evaluating a marker in a patient population having breast cancer to assess the value of the marker in a patient population that does not yet have breast cancer. See, e.g., page 2716 of Tockman et al. which discusses diagnosing cancer "well in advance of clinical cancer". Thus, Tockman et al. were deriving their data from a patient population, i.e., patients having breast cancer, different than the patient population in which the marker was going to be used, i.e., patients not yet diagnosed with clinical cancer. In contrast, Applicant's data was derived from the same patient population as that in which the marker will be used, namely patients diagnosed with prostate cancer. Therefore, the need for prospective patient population validation for Tockman et al. and Vandesompele et al., does not translate to a need for such information for the present invention.

The Office states that

> Similar to the unknown population of patients not yet diagnosed with breast cancer to be tested and validated, as taught by Tockman et al, the instant claims also encompass PSMA predictive value for a population not previously tested by the instant application, i.e., any prostate cancer population, including those with low grade prostate cancer.

As discussed above in section II, Applicant's findings and the findings of Perner et al. (which corroborates Applicant's findings) were based upon analysis of PSMA expression levels in patients having both low grade and high grade prostate cancer. Therefore, contrary to the statements made by the Office, the patient population evaluated by Tockman et al. (or Vandesompele et al.) is not similar to the patient population analyzed by the Applicant.

VII. Based upon the teaching in the application and the knowledge in the art at the time of filing, the reference standard can be determined without undue experimentation

The Office asserts that "one would not know how to perform the claimed method because one cannot predict which actual level of PSMA is the value for the claimed reference standard."

Applicant respectfully disagrees. The present application provides detailed disclosure of the statistical analysis used to determine that there is a significant difference is PSMA expression levels at the time of diagnosis that correlates with the risk of recurrence at a later date. These differences are depicted, for example, in Figures 3 and 4 of the application. Thus, there is sufficient description in the present application to allow one of ordinary skill in the art to determine the reference standard.

In addition, the knowledge in the art at the time of filing would allow one of ordinary skill in the art to determine a reference standard without undue experimentation. The art is replete with examples of skilled artisans determining statistically significant differences in PSMA expression levels in order to establish a reference standard. For example, Bostwick et al., Beckett et al., Thomas et al., etc. all disclose using statistical analysis to establish a baseline standard from which the PSMA levels can be evaluated.

In view of the overwhelming evidence to support Applicants' finding (in contrast to the one ten year old reference cited by the Office that relies upon subjective analysis), there is sufficient guidance provided in the present application to enable to claimed invention. Therefore, the Applicant respectfully requests that this rejection be withdrawn.

CONCLUSION

For at least the reasons stated above, Applicant respectfully submits that all examined claims are in condition for allowance, which action is expeditiously requested. Applicant does not concede any positions of the Office that are not expressly addressed above, nor does the Applicant concede that there are not other good reasons for patentability of the presented claims or other claims.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicants hereby request any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, please charge any deficiency to Deposit Account No. 50/2762.

Respectfully submitted,

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